(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 July 2002 (25.07.2002)

PCT

(10) International Publication Number
WO 02/057475 A1

(51) International Patent Classification[7]: C12P 13/00, 41/00, C12N 9/18

(21) International Application Number: PCT/IN01/00008

(22) International Filing Date: 22 January 2001 (22.01.2001)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant *(for all designated States except US)*: **COUNCIL OF SCIENTIFIC AND INDUSTRIAL RESEARCH** [IN/IN]; an Indian Registered body incorporated under the Registration of Societies Act (Act XXI of 1860), Rafi Marg, New Delhi 110 001 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KAMAL, Ahmed** [IN/IN]; Indian Institute of Chemical Technology, Hyderabad, Andhra Pradesh 500 007 (IN). **KHANNA, Gollapalli, Bhasker** [IN/IN]; Indian Institute of Chemical Technology, Hyderabad, Andhra Padesh 500 007 (IN). **RAO, Maddamsetty, Venkate** [IN/IN]; Indian Institute of Chemical Technology, Hyderabad, Andhra Pradesh 500 007 (IN). **RAGHAVAN, Kondapuram, Vijaya** [IN/IN]; Indian Institute of Chemical Technology, Hyderabad, Andhra Pradesh 500 007.(IN).

(74) Agent: **GABRIEL, Devadoss, Calab**; Kumaran & Sagar, 84-c C6 Lane, Sainik Farms, New Delhi 110 062 (IN).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *with amended claims and statement*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/057475 A1

(54) Title: STEREOSELECTIVE PREPARATION OF 3-HYDROXY-3-PHENYLPROPIONITRILE

(57) Abstract: This invention relates to a Chemoenzymatic process for the stereoselective preparation of both (R) and (S) enantiomers of 3-hydroxy-3-phenylpropanenitrile, useful as a key intermediate for synthesis of (S)-fluoxetine, (R)-tomoxetine and cognant compounds, which comprises reacting cyanohydrin with an acetylating agent in the presence of lipase in an organic solvent, followed by separation of (R)-acetate and (S) alcohol, hydrolyzing (R)-acetate in presence K2CO3 in methanol, filtering the reaction mixture and evaporating the solvent to obtain the (R) alcohol.

STEREOSELECTIVE PREPARATION OF 3-HYDROXY-3-PHENYLPROPIONITRILE

Technical Field

The present invention relates to a chemoenzymatic process for the stereoselective preparation of both R and S enantiomers of 3-hydroxy-3-phenylpropanenitrile.

This invention particularly relates to a chemoenzymatic process for the stereoselective preparation of both (R) and (S) enantiomers of 3-hydroxy-3-phenylpropanenitrile a key intermediate for the synthesis of antipsychic drugs like (S)-fluoxetine and (R)-tomoxetine.

Background Art

Fluoxetine, tomoxetine and related class of compounds are important for treating psychiatric disorders (Figure-1 of accompanying drawing). Tomoxetine is a norepinephrine reuptake inhibitor where as fluoxetine is a neuronal inhibitor of serotonin reuptake and are clinically effective in treating depression. Fluoxetine in particular is a multifaceted drug used in treating migraine headache, chronic pain, obsessive compulsive disorders, sexual disfunctioning, memory disorders, sleep disorders etc.

Although fluoxetine and tomoxetine and their cognant compounds nisoxetine and norfluoxetine are therapeutically used in racemate form (*Analytical Profiles of Drug Substances*, vol. 19, p.193-219; Klaus Florey, Ed; Academic Press Inc., San Diego, 1990 and references cited therein), while there is some stereospecificity associated with their biological action. The current preference is for the use of enantiomerically pure drugs due to differences in metabolic behaviour and pharmacological activities displayed by individual enantiomers.

Fluoxetine and tomoxetine have the same basic structural skeleton of 3-amino-propanol, but the need is for different enantiomers of high optical purity. These enantiomerically pure compounds have been prepared by using optically pure substrates (*Synth. Commun.*, 1995, *25*, 1231) or by employing a chiral reducing agents (*J. Org. Chem.*, 1988, *53*, 2916; *J. Org. Chem.*, 1988, *53*, 4081) or by chemoenzymatic synthesis. In chemoenzymatic synthesis either an oxo group is reduced by whole cells or microorganism (*Tetrahedron Lett.*, 1991, *32*, 1901; *Chem. Lett.*, 1991, 1603) or by kinetic resolution of 3-chloro-1-phenyl-1-propanol (*Tetrahedron:Asymmetry*, 1992, *3*, 525) or 1-phenyl-3-buten-1-ol (*Tetrahedron Lett.*, 1996, *37*, 9253) using lipases. The reported methods employ chiral reducing agents and usually these reagents are not commercially available. Some methods involve tedious work-up procedure while others employ expensive starting materials.

Disclosure of the invention

The main objective of the present invention is to provide a chemoenzymatic process for the stereoselective preparation of both (R) and (S) enantiomers of 3-hydroxy-3-phenylpropanenitrile.

Another objective of the present invention is to employ vicinal cyanohydrin as the substrate.

Summary of the invention

Accordingly, the present invention provides a chemoenzymatic process for the stereoselective preparation of both (R) and (S) enantiomers of 3-hydroxy-3-phenylpropanenitrile which are the optically pure intermediates for the synthesis of (S)-fluoxetine and (R)-tomoxetine in high enantiomeric excess as they are promisingly more potent than their other enantiomers with less affinity for β-adrenergic receptors.

Also, the present invention employs vicinal cyanohydrin as the substrate of choice, which is the key intermediate for the antianxiety and antidepressant drugs.

Detailed Description of the invention

Accordingly, the present invention provides an enzymatic process for the stereoselective preparation of both (R) and (S) enantiomers of 3-hydroxy-3-phenylpropanenitrile, a key intermediate for the synthesis of (S)-fluoxetine, (R)-tomoxetine and cognant compounds which comprises of reacting the cyanohydrin with acetylating agent in the presence of lipase followed by separation of (R)-acetate and (S)-alcohol obtained and by hydrolysing (R)-acetate in the presence of K_2CO_3 in methanol to obtain the required enantiomers.

In an embodiment of the present invention 3-hydroxy-3-phenylpropanenitrile (6) is formed by facile regioselective ring opening of styrene oxide (5) with alkali metal cyanide selected from sodium cyanide and potassium cyanide.

In another embodiment of the present invention, the 3-hydroxy-3-phenylpropanenitrile is selectively acetylated with vinyl acetate, isopropenyl acetate in the presence of lipases.

In yet another embodiment of the present invention the alcohol and the ester formed in the kinetic resolution are separated by column chromatography, absolute configuration is ascertained by the values of optical rotation, and the enantiomeric purity was confirmed by HPLC employing chiral column.

In an embodiment of the present invention, sodium cyanide in aqueous alcoholic conditions is used as a source for cyanide for the nucleophilic rings opening.

In yet another embodiment of the present invention, 3-Hydroxy-3-phenylpropanenitrile is

prepared by regioselective ring opening of styrene oxide between 20-40°C by stirring for 8-10 hrs.

In yet another embodiment of the present invention, the reaction mixture is concentrated to about half the volume followed by extraction with ethyl acetate and this upon evaporation gave the residue.

In yet another embodiment of the present invention, the residue thus obtained is purified by column chromatography to give 3-hydroxy-3-phenylpropanenitrile more than 98 % yield.

In yet another embodiment of the present invention, the racemic 3-hydroxy-3-phenylpropanenitrile is acetylated enzymatically employing different acetylating agents and various lipases in different solvents.

In yet another embodiment of the present invention, the acetylating agent is selected from vinyl acetate and isopropenyl acetate.

In yet another embodiment of the present invention, the lipase used is selected from *Pseudomonas cepacia* lipase (Amano PS), *Candida rugosa* lipase (CRL) and *Porcine pancreas* lipase (PPL).

In yet another embodiment of the present invention, the organic solvent is selected from the group consisting of diisopropyl ether, t-butylmethyl ether, diethyl ether, tetrahydrofuran, and toluene.

In yet another embodiment of the present invention, the presence of lipase (R)-3-hydroxy-3-phenylpropanenitrile is selectively acetylated and the (R)-acetate and the (S)-alcohol are separated by column chromatography.

In yet another embodiment of the present invention, the enantiomeric excess is determined by HPLC employing chiral column.

In yet another embodiment of the present invention, the synthesis of (S) fluoxetine and (R) tomoxetine is performed conventionally.

Brief description of the accompanying drawings:

Figure-1 represents the structures of norfluoxetine, fluoxetine, tomoxetine and nisoxetine

Figure-2 shows the schematic representation of this process towards the preparation of both enantiomers of 3-hydroxy-3-phenylpropanenitrile and their usefulness towards the synthesis of (S)-fluoxetine and (R)-tomoxetine.

The following examples are given by way of illustration and they should not be construed to limit the scope of the present invention.

Example 1

Preparation of 3-Hydroxy-3-phenylpropanenitrile: To a solution of styrene oxide (10 mmol) in ethanol (10-15 mL) water (50 mL) was added and stirred for 5 minutes. To this sodiumcyanide (12 mmol) was added and stirring was continued for 6-8hrs. After formation of the product as indicated by TLC, the reaction mixture was concentrated to about half the volume under reduced pressure. The residue was extracted with ethyl acetate washed with brine and dried over anhydrous sodium sulphate to give the product. This was further purified by column chromatography employing EtOAc/hexane as the eluent. (Yield 95%). ^{1}H NMR ($CDCl_3$); 7.35 (s, 5H), 4.90-5.0 (t, 1H), 2.65-2.70 (d, 2H); MS: m/z 147(M^+).

Example 2

Enzymatic Resolution of (S)-3-hydroxy-3-phenylpropanenitrile and its (R) acetate: To a solution of 3-hydroxy-3-phenylpropanenitrile (5 mmol) dissolved in diisopropyl ether (100 mL), *Pseudomonas cepacia* lipase (600 mg) and vinyl acetate (10 mmol) were added successively and incubated at 40^{0}C in an orbital shaker. After 50% completion of the reaction (72-78 hrs) as indicated by TLC, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The residue was subjected to column chromatography to separate the ester and the unreacted alcohol. The optical purity of these compounds were determined by HPLC. Yield of (S)-3-hydroxy-3-phenylpropanenitrile 49%, ee >99%; $[\alpha]^{20}_D$ –60.5 (c 1, $CHCl_3$); Yield of (R) acetate(2-cyano-1-phenyl-1(R)-ethyl acetate) 48%, ee >99%, $[\alpha]^{20}_D$ +71.9 (c 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$);7.35 (s, 5H), 5.85-5.95 (t, 1H), 2.80-2.90 (d, 2H), 2.15 (s, 3H); MS: m/z 189 (M^+); m.p. 97-100°C.

Example 3

Hydrolysis of (R)-acetate to (R)-3-Hydroxy-3-phenylpropanenitrile: To a solution of (R)-acetate (3 mmol) in 30 mL of methanol was added K_2CO_3 (10 mmol) and stirred at room temperature for 6 hrs. After complete hydrolysis of ester as indicated by TLC, the reaction mixture was subjected to filteration. The residue is treated with ethyl acetate (2x15ml). The organic layers was combined and solvents were evaporated to get the (R)-3-hydroxy-3-phenylpropanenitrile in almost quantitative yields (98%), e.e > 99%.

Example 4

Chiral HPLC Analysis: HPLC analysis was performed by employing chiral column (Chiralcel OD, Daicel). The racemic acetate was prepared by treating 3-hydroxy-3-phenylpropanenitrile with acetic anhydride in presence of pyridine as an authentic sample

for comparison on HPLC. The mobile phase was hexane: isopropanol (90:10), flowrate 0.5 mL/min and monitored at UV 254 nm.

The main advantages of the present invention are:

Vicinal cyanohydrins or 1,2-cyanohyrins are important and versatile compounds in organic synthesis as they could be easily transformed to amino alcohols, hydroxy amides, hydroxy esters, hydroxy acids etc., by employing simple methods. In recent years there has been an increasing demand for the optically pure forms of these vital intermediates which could lead to chirally pure compounds of biological importance.

3-hydroxy-3-phenylpropanenitrile has been obtained by regioselective ring opening of styrene oxide in good yields. This is an exceptionally mild and simple procedure, which is carried out at 20-40^{0}C. In this process chiral 1,2-cyanohydrin has been obtained by lipase mediated resolution in high enantiomeric excess.

Claims

1) A chemoenzymatic process for the stereoselective preparation of both (R) and (S) enantiomers of 3-hydroxy-3-phenylpropanenitrile, useful as a key intermediate for synthesis of (S)-fluoxetine, (R)-tomoxetine and cognant compounds, which comprises reacting cyanohydrin with an acetylating agent in the presence of lipase in an organic solvent, followed by separation of (R)-acetate and (S) alcohol, hydrolyzing (R)-acetate by adding K_2CO_3, in methanol, filtering the reaction mixture and evaporating the solvent to obtain the (R) alcohol and thereby obtaining the required enantiomers.

2) A process as claimed in claim 1 wherein, the cyanohydrin is obtained by reacting styrene oxide with a alkali metal cyanide selected from sodium cyanide and potassium cyanide.

3) A process as claimed in claim1 wherein, Hydroxy-3-phenylpropanenitrile is prepared at a mild simple procedure, which is carried out a temperature ranging between 20-40°C and stirring for 8-10 hrs.

4) A process as claimed in claim 1 wherein, recycling is not required for these products as they are obtained by kinetic resolution since the enantiomeric excess is >99%.

5) A process as claimed in claim 1 wherein, the residue thus obtained is purified by column chromatography to give 3-hydroxy-3-phenylpropanenitrile more than 98 % yield.

6) A process as claimed in claim 1 wherein, the acetylating agent employed is selected from vinyl acetate and isopropenyl acetate.

7) A process as claimed in claim 1 wherein, the organic solvent used is selected from the group consisting of diisopropyl ether, t-butylmethyl ether, diethyl ether, tetrahydrofuran, methanol and toluene.

8) A process as claimed in claim 1 wherein, the lipase used is selected from *Pseudomonas cepacia* lipase (Amano PS), *Porcine pancreas* lipase (PPL) and *Candida rugosa* lipase (CRL).

9) A process as claimed in claim 1 wherein, the synthesis of (S) fluoxetine and (R) tomoxetine is performed conventionally.

AMENDED CLAIMS

[received by the International Bureau on 17 May 2002 (17.05.02);
original claims 1-9 replaced by new claims 1-12 (2 pages)]

Claims:

1) A chemoenzymatic process for the stereoselective preparation of both (R) and (S) enantiomers of 3-hydroxy-3-phenylpropanenitrile, useful as a key intermediate for synethesis of (S)-fluoxetine, (R)-tomoxetine and cognant compounds, the said process comprising the steps of:
   a) reacting styrene epoxide with alkali cyanide in presence of an alcohol at an ambient temperature to obtain the cyanohydrin,
   b) treating the cyanohydrin of step (a) with an acylating agent in the presence of lipase enzyme in an organic solvent to obtain a mixture of (R)-3-acetoxy and (S)-3-hydroxy-3-phenylpropionitrile,
   c) purifying the products of step (b) to obtain (R)-3-acetoxy phenylpropionitrile and (S)-3-hydroxyphenylpropionitrile,
   d) hydrolysing (R)-3-acetoxy phenylpropionitrile of step (c) with alkali carbonate and alcohol at a temperature ranging between 20 ° to 40 ° C for a period of 8-10 hrs, and
   e) filtering the reaction mixture of step (b), evaporating the filtrate, filtering the solid thus obtained to yield (R)-3-hydroxy-3-phenyl propionitrile of required enantiomeric purity.
2) A process as claimed in claim 1, wherein in step (a) the alkali metal cyanide used is selected from a group consisting of sodium cyanide and potassium cyanide.
3) A process as claimed in claim 1, wherein in step (a) the alcohol used is selected from methanol, ethanol or isopropanol and preferably methanol.
4) A process as claimed in claim 1, wherein the (R) and (S) isomer of 3-hydroxy-3-phenyl propionitrile is prepared by simple procedure under a mild condition.
5) A process as claimed in claim 1, wherein in step (b) the acylating agent is selected from vinyl acetate or isoprenyl acetate.
6) A process as claimed in claim 1, wherein in step (b) the lipase enzyme used is selected from Pseudomonas cepacia lipase (Amano PS), Porcine pancreas lipase (PPL) and Candida rugosa lipase (CRL).

7) A process as claimed in claim 1, wherein in step(b) the organic solvent used is selected from a group consisting of diisopropyl ether, t-butylmethyl ether, diethyl ether, tetrahydrofuran, methanol and toluene.

8) A process as claimed in claim 1, wherein in step (c) (R)-3-hydroxy-3-phenyl propiontrile is obtained in a yield of more than 98 %

9) A process as claimed in claim 1, wherein in step (d) the alkali carbonate used is selected from a group consisting of sodium bicarbonate, sodium carbonate, potassium bicarbonate or potassium carbonate and preferably potassium carbonate.

10) A process as claimed in claim 1, wherein in step (d) the alcohol used is selected from a group consisting of methanol, ethanol or isopropanol and preferably methanol.

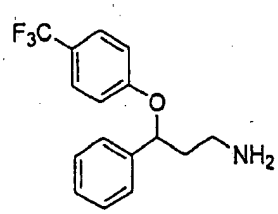
11) A process as claimed in claim 1, wherein the (R) and (S) isomers of 3-hydroxy-3-phenyl propionitrile does not require recycling for purification as they are obtained by kinetic resolution having an enantiomeric excess greater than 99%.

12) A process as claimed in claim 1, wherein the synthesis of (S)-fluoxetine and (R)-tomoxetine is performed conventionally.

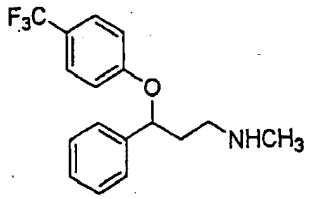
STATEMENT UNDER ARTICLE 19 (1)

The claims have been revised to make them more clear and definite. No new matter has been added in the revised claims. While revising the claims, the novel and non-obvious features such as preparation of racemic 3-Phenyl-3-hydroxy-propionitrile starting from styrene epoxide is not inferred, which is the starting material in the present invention and hydrolysis of the optically active (R)-3-acetoxy-3-phenyl propionitrile, using potassium carbonate and methanol to obtain R(-) alcohol retaining high enantiomeric purity has been outlined.

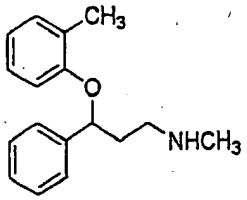
Though, the method for the preparation of (R)-acetate of 3-Phenyl-3-hydroxy-propionitrile can be inferred by these citations, but its hydrolysis using K_2CO_3/methanol cannot be envisaged in this citation. Use of an enzyme for the hydrolysis of acetyl function and a base for the same purpose provides a very different reaction condition to perform the hydrolysis of acetyl group to obtain the hydroxyl group. Use of an inorganic base to hydrolyze the acetyl group need not necessarily provide specificity in retaining the optical activity of the starting material. The hydrolysis carried out by chemical reaction conditions are known to destroy the optical active center by encountering inversion at the optically active center leading to racemic product. Thus, by overcoming this major problem of inversion, which is the main objective of the present invention and obtaining the optically active enantiomer having high purity, by using inexpensive and commonly available chemical is a significant achievement in the present invention.



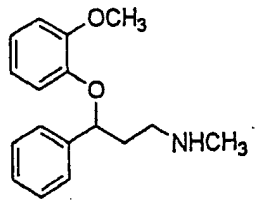
1. Norfluoxetine



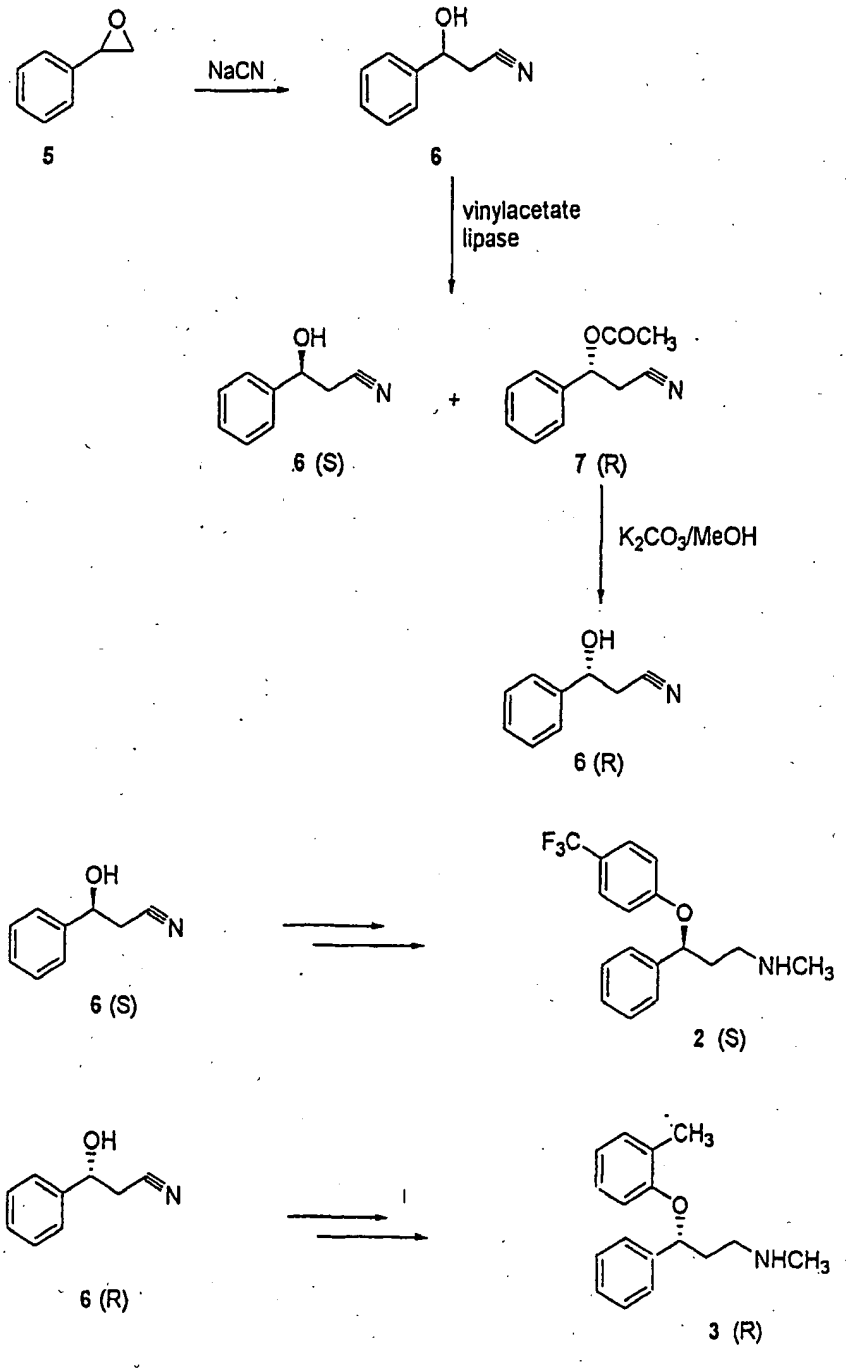
2. Fluoxetine



3. Tomoxetine



4. Nisoxetine


NaCN
5
6
vinylacetate
lipase
6 (S)
7 (R)
K_2CO_3/MeOH
6 (R)
6 (S)
2 (S)
6 (R)
3 (R)

INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/IN 01/00008

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12P13/00 C12P41/00 C12N9/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12P C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, CHEM ABS Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ITOH, TOSHIYUKI ET AL: "Enhanced enantioselectivity of an enzymatic reaction by the sulfur functional group. A simple preparation of optically active.beta.-hydrox nitriles using a lipase" J. ORG. CHEM., vol. 56, no. 4, 1991, pages 1521-1524, XP002179192 table II --- -/--	1-9

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 October 2001	17/10/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lejeune, R

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SAKAI T ET AL: "Lipase-Catalyzed Efficient Kinetic Resolution of 3-Hydroxy-3-(pentafluorophenyl)propionitrile" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 38, no. 11, 17 March 1997 (1997-03-17), pages 1987-1990, XP004055834 ISSN: 0040-4039 the whole document	1-9
A	MASTER HOSANG E ET AL: "Highly efficient enzymatic resolution of homoallyl alcohols leading to a simple synthesis of optically pure fluoxetine and related compounds." TETRAHEDRON LETTERS, vol. 37, no. 51, 1996, pages 9253-9254, XP004070613 ISSN: 0040-4039 cited in the application the whole document	1-9
A	WANG Y-F ET AL: "LIPASE-CATALYZED IRREVERSIBLE TRANSESTERIFICATION USING ENOL ESTERS RESOLUTION OF CYANOHYDRINS AND SYNTHESES OF ETHYL-R-2-HYDROXY-4-PHENYLBUTYRATE AND S PROPRANOLOL" TETRAHEDRON LETTERS, vol. 30, no. 15, 1989, pages 1917-1920, XP002179194 ISSN: 0040-4039 the whole document	1-9
A	EFFENBERGER F ET AL: "ENZYME-CATALYZED REACTIONS 7. ENANTIOSELECTIVE ESTERIFICATION OF RACEMIC CYANOHYDRINS AND ENANTIOSELECTIVE HYDROLYSIS OR TRANSESTERIFICATION OF CYANOHYDRIN ESTERS BY LIPASES" LIEBIGS ANNALEN DER CHEMIE, no. 1, 1991, pages 47-54, XP002179195 ISSN: 0170-2041 schema 3 table 3	1-9